22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures 5A-5B or Table 4, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

REMARKS

Claims 1-25 are pending in this application. Claims 1-6 and 15-23 were considered and rejected under 35 U.S.C. §§ 101 and 112 in the Office Action of July 29, 2002. Claims 7-14 and 24-25 have been withdrawn from consideration in response to Applicants' election of Specie A (claims 1-6 and 15-23). A copy of Claims 1-6 and 15-23 as amended herein is attached for the Examiner's convenience as Appendix C.

The Office Action stated that the application did not comply with the sequence listing rules because there were sequences on page 43 that were not listed. Applicants have submitted herewith a Substitute Sequence Listing which contains those sequences and a Statement Under 37 C.F.R. § 1.821(f). The Substitute Sequence Listing has two sequences (SEQ ID Nos. 3 and 4) which were not previously in the Sequence Listing but correspond to the sequences on the last three lines of page 43. Applicants have also amended page 44 of the specification to include the correct SEQ ID Nos. set forth in the Sequence Listing, in that Applicants have renumbered the Sequence Listing so that the numbering of sequences is sequential as they appear in the specification (that is, the SEQ ID Nos. on page 43 will numerically precede those SEQ ID Nos. on page 44).

The Office Action stated that, if Applicants desired priority under 35 U.S.C. §120 based on a previously filed copending application, specific reference to earlier filed

application must be made, including the status of the application. Applicants have amended the first paragraph on page 1 of the specification to set forth a priority claim to an earlier filed PCT application and an earlier filed U.S. application.

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph, as indefinite as referring to Figure 2-20. Applicants' amendment to correct this typographical error has rendered this rejection moot. Claim 22 now refers to Figures 5A-5B and Table 4.

Claims 1-6 and 15 were also rejected under 35 U.S.C. § 112, second paragraph, as indefinite. It was the Examiner's position that those claims provide for "the use of atomic coordinates of BPI etc., for modeling, but, since the claim allegedly does not set forth any actual steps involved, it is unclear what applicants are intended to encompass." (Office Action, page 3). The same claims were also rejected under 35 U.S.C. § 101, and the Examiner stated "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101." (Office Action, page 4).

Applicants respectfully disagree and submit that each of claims 1-6 and 15 sets forth an active, positive step. Applicants have amended claims 1 and 2 to specifically refer to the step of using atomic coordinates to generate a three-dimensional structural representation of the BPI protein or the BPI-related lipid transfer protein. The Examiner asserts that the present claims differ from those allowed in *Ex parte Bouillon,* 1998 WL 1744151 (Bd. Pat. App. & Interf. 1998) (unpub.). The Examiner stated that the fact pattern of *Bouillon* is very different because those claims required a "physical bringing together or applying." Applicants do not believe this was the dispositive rationale for allowing the claim in *Bouillon.* The Board found it dispositive that the claim recited a positive step, and claims 1-6 and 15 of the present application also recite a positive step.

Claims 1-6 and 15-23 were also rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Claims 1-6 and 15-20 are directed to methods of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein or BPI-related lipid transfer protein. Claims 21-22 are directed to methods for providing an atomic model of a BPI protein, or fragment, analog or variant thereof. Claim 23 is directed to computer-based systems for providing atomic model data of the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment. As such, the claims provide three-dimensional structural representations, models or model data for the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment. The Examiner admits that the subject matter of claims 1-6 and 15-23 is potentially useful in drug design. (Office Action, page 5). Such models are more tangible and concrete than the result of the "transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price," which was held to be patentable subject matter in *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998). Providing such models or model data is a "useful, concrete and tangible result", and therefore constitutes statutory subject matter.

Claims 1-6 and 16-23 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner acknowledged that the claims were enabled for BPI protein of SEQ ID NO: 1. However, it was the Examiner's position that the specification does not reasonably provide enablement for any other BPI protein, fragment, analog or variant without three-dimensional coordinates as in Table 4. Applicants respectfully disagree and assert that the claims are fully enabled and definite for the reasons outlined below.

The Examiner has asserted that "crystallization of a protein in order to obtain suitable crystals for X-ray crystallography is a trial and error process." The Examiner cites only the first few lines of Drenth (a collegiate textbook), which provide a broad generalization. The

Examiner's reliance on Drenth is misplaced. The pending claims are not to protein crystals or methods of crystallization of proteins, but rather are directed to methods of modeling and providing an atomic model, as well as to computer-based systems for providing atomic model data of the three-dimensional structure. As such, these claims are enabled by the detailed information regarding the binding pockets of BPI protein set forth in Table 3, the atomic coordinates of BPI set forth in Table, as well as the specification as a whole.

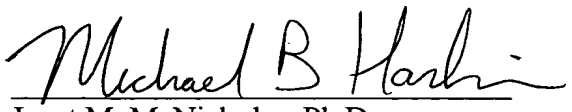
The Examiner objected to certain informalities, namely, that the Figure designations on pages 14-15 of the specification differed from the actual Figures in that the designation 1A was in the Figure whereas 1(A) was set forth on page 14. Applicants have amended the specification's brief description of the drawings so that the designations are consistent with those of the Figures.

Applicants respectfully submit that the rejections to claims 1-6 and 15-23 under § 112 and § 101 may properly be withdrawn in view of the amendments and remarks herein.

The Commissioner is hereby authorized to charge Account no. 13-0017 (McAndrews, Held & Malloy) for any fee deficiency, or credit any overpayment associated with this application.

In view of the foregoing amendments and remarks, Applicants submit that a complete response has been made to the Office Action and that the claims as amended herein are in condition for allowance. The Examiner is invited to telephone Applicants' undersigned representative if the Examiner believes, for any reason, that personal communication would expedite prosecution of this application.

Respectfully submitted,



Dated: January 29, 2003

Janet M. McNicholas, Ph.D.
Registration No. 32,918
Michael B. Harlin
Registration No. 43,658

McAndrews, Held & Malloy, Ltd.
500 West Madison Street, 34th Floor
Chicago, Illinois 60661
(312) 775-8000 (Telephone)
(312) 775-8100 (Facsimile)

Appendix A
Changes Made to The Specification
(Deletions in brackets, additions underlined)

Page 1, lines 5-7:

This **application is a §371 national phase application from International Application No. PCT/US98/13007, filed June 22, 1998, which** is a continuation-in-part application of U.S. Application Serial No. 08/879,565, filed June 20, 1997, **now U.S. Patent No. 6,093,573,** which is hereby incorporated by reference in its entirety.

Page 14, lines 7-30, and page 15, lines 1-28:

Fig. 1[(A)]A A ribbon diagram of residues 1-456 of BPI illustrating its boomerang shape. The NH_2-terminal domain is shown; the COOH-terminal domain and the two phosphatidylcholine molecules are shown. The linker is also shown, and the disulfide bond is shown as a ball-and-stick model. **[(B)] Fig. 1B** View after rotating Fig. 1A [(A)] 70° about the long axis of the molecule. Figure produced with MOLSCRIPT [P. Krauliz, *J. Appl. Cryst., 24*:926 (1991)] and RASTER3D [E. A. Merrit and M. E. P. Murphy, *Acta Crystallogr., D50*:889 (1994); D. J. Bacon and W. F. Anderson, *J. Mo. Graphics, 6*:219 (1988)].

Fig. 2[(A)]A Schematic drawing of the novel BPI domain fold, shown in same orientation as the NH_2-terminal domain in Fig. 1**B.** **[(B)] Fig. 2B** Superposition of the NH_2- and COOH-terminal domains of BPI showing the overall topological similarity. Residues 1 to 230 and 250 to 456 are shown. The NH_2-terminal domain is in the same orientation as Fig. 1A.

Fig. 3 Electron density of the final 2.8 Å MIR map contoured at 1.0 σ and superimposed on the refined model. The area shown is in the lipid binding pocket of the NH_2-terminal domain of BPI. The phosphatidylcholine and the surrounding protein atoms are shown.

Fig. 4[(A)]A The covalent structure of phosphatidylcholine and the lipid A region of LPS from *E. coli and S. typhimurium*. Phosphate groups are indicated by P. Adapted with changes from [C. R. H. Raetz, *Annu. Rev. Biochem, 59*:129 (1990+)]. **Fig. 4[(B)]B** Slice through the interior of BPI

showing the lipid binding pocket in the NH_2-terminal domain. The solvent accessible surface of the protein was calculated without lipid present, the interior of the protein and the phosphatidylcholine are shown. Protein residues are shown as ball-and-stick.
Figure produced with MSP [M. L. Connolly, *Science, 221*:709 (1983); M. L. Connolly, *J. Am. Chem. Soc., 107*:1118 (1985)].

Figs. 5[(A)]A and **5[(B)]B** The amino acid sequences of human BPI (SEQ ID NO: 3), LBP (SEQ ID NO: 4), PLTP (SEQ ID NO: 5), and CETP (SEQ ID NO: 6). The alignment was performed with CLUSTAL [D. G. Higgins and P. M. Sharp, Gene, 73:237 (1989)] using all eleven known protein sequences from mammals [R. R. Schuman, et al., Science, 249:1429 (1990); D. Drayna et al., Nature, 327:632 (1987); R. Day et al., J. Biol. Chem., 269:9388 (1994); S. R. Leong and T. Camerato, Nucleic Acids Res., 18:3052 (1990); M. Nagashima, J. W. McLean, R. M. Lawn, J. Lipid Res., 29:1643 (1988); M. E. Pape, E. F. Rehber, K. R. Marotti, G. W. Melchior, Artheriosclerosis 11:1759 (1991); G. Su et al., J. Immunol., 153:743 (1994); P. W. Gray et al., J. Biol. Chem. 264: 9505 (1989); Albers et al., Biochem. Biophys. Acta, 1258:27 (1995); X. C. Jiang et al., Biochemistry, 34:7258 (1995); L. B. Agellon et al., Biochemistry, 29:1372 (1990); X. C. Jiang et al., J. Biol. Chem., 266:4631 (1991)] but only the four human sequences are shown. Residues that are completely conserved in all proteins are indicated below the sequence *; those which are highly conserved are indicated by •. The secondary structure of BPI is indicated above the sequences. The β strands are indicated by arrows; strands which make up the central β sheet are shown with gray arrows. Because of the β bulges and pronounced twisting, some of the β strands have one or more residues that do not show classical H-bonding patterns or ΦΨ angles; these breaks are indicated by ^ above the strands. The α helices are shown as cylinders, and one-residue breaks in helices B and B' are indicated with a vertical dashed line. The horizontal dashed line indicates the linker region. Peptides from BPI and LBP with the highest lipopolysaccharide-binding activity (Little, et al., J. Biol. Chem. 268: 1865 (1994); Taylor et al., J. Biol. Chem. 270: 17934 (1995)) are in bold italics. The disulfide bond is indicated by S-S. Residues with atoms within 4 Å of the NH_2 -terminal lipid are highlighted with gray shading; residues within 4 Å of the COOH-terminal lipid are shown with white letters in black boxes.

Page 43, line 27 to page 44, line 6:

To allow insertion of BPI into an optimized mammalian expression vector, a unique *Xho*I site was first added to the 3′ end of the BPI gene in pIC108. Two oligonucleotides were synthesized for this purpose: BPI-53 (5′ ACT GGT TCC ATG GAG GTC AGC GCC 3′) **(SEQ ID NO: 7)** encoding amino acids 361 - 370 of BPI and BPI-54 (5′ GAC AGA TCT CTC GAG TCA TTT ATA GAC AA 3′) **(SEQ ID NO: 8)** encoding the last four amino acids of coding sequence, the stop codon (TGA), and incorporating an *Xho*I site immediately downstream of the stop codon. These oligonucleotides were used to PCR amplify a 280 bp fragment of the C-terminus of BPI and incorporate the *Xho*I site at the 3′ end of the gene. The amplified fragment was digested with *Nco*I and *Bgl*II and ligated to a ~4100 bp [NcoI-BamHI] *Nco*I-*Bam*HI fragment from pIC108 to generate the plasmid pSS101.

Page 44, lines 8-24:

The glycosylation site was next removed by replacing the region from a unique *Xcm*I site to a unique *Sph*I site within the BPI gene in pSS101 with an annealed oligonucleotide that contained the codon (TCC) for the serine at amino acid position 351 changed to the codon (GCC) for alanine as shown below.

```
Wild type
     XcmI                                          SphI
...CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC (SEQ ID NO:7)9)
...GGG TTG AGG AGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG (SEQ ID NO:8)10)
   Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His (SEQ ID NO:9)11)
               351
Nonglycosylated
     XcmI                                          SphI
...CCC AAC TCC GCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC (SEQ ID NO:10)12)
...GGG TTG AGG CGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG (SEQ ID NO:11)13)
   Pro Asn Ser Ala Leu Ala Ser Leu Phe Leu Ile Gly Met His (SEQ ID NO:12)14)
               351
```

This step generated the plasmid pSS102.

Appendix B
Changes Made to Claims 1-2 and 22
(Deletions in brackets, additions underlined)

1. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to **[model]** **generate a three-dimensional structural representation of** the BPI protein.

2. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to **[model]** **generate a three-dimensional structural representation of** the BPI-related lipid transfer protein.

22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures **[2-20]** **5A-5B** or Table **[2]** **4**, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

Appendix C
Specie A Claims 1-6 and 15-23
of U.S. Application No. 09/446,415

1. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to generate a three-dimensional structural representation of the BPI protein.

2. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to generate a three-dimensional structural representation of the BPI-related lipid transfer protein.

3. The method according to claim 2, wherein the BPI-related lipid transfer protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

4. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

5. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

6. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about

45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

15. The method according to any of claims 1 – 3, wherein said atomic coordinates are according to Table 4.

16. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI protein suitable for visualization and further computational manipulation.

17. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI")-related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI-related lipid transfer protein suitable for visualization and further computational manipulation.

18. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

19. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

20. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

21. A method for providing an atomic model of a BPI protein, or fragment, analog or variant thereof, having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising

(a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of the BPI protein, or fragment, analog or variant thereof, in crystalline form, the data sufficient to model the three-dimensional structure of the BPI protein, or fragment, analog or variant thereof;

(b) analyzing, on a computer using at least one subroutine executed in said computer, atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) obtaining atomic coordinate data defining the three-dimensional structure of at least one of said BPI protein, or fragment, analog or variant thereof.

22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures 5A-5B or Table 4, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

23. A computer-based system for providing atomic model data of the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment, having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the system comprising the following elements:

(a) at least one computer readable medium (CRM) having stored thereon atomic coordinate/x-ray diffraction data of said BPI protein, or fragment, analog or variant thereof;

(b) at least one computing subroutine that, when executed in a computer, causes the computer to analyze atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) retrieval means for obtaining atomic coordinate output data substantially defining the three-dimensional structure of said BPI protein, or fragment, analog or variant thereof.